Intrachromosomal Looping Is Required for Activation of Endogenous Pluripotency Genes during Reprogramming.

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Public Summary:
Generation of induced pluripotent stem cells (iPSCs) depends on the synthesis of factor proteins that regulate the developmental clock of adult cells in order to return them to the embryonic state. However, the efficiency of iPSC induction is extremely low with all existing approaches. To fundamentally improve this technology, we examined the epigenetic barrier that limits the generation of iPSCs. We first compared the binding of these factors to their target gene promoters. It was surprised to find that these factors bound to their target promoters equally in both iPSCs and non-iPSCs. We then examined the local chromatin structure and found that the formation of chromatin loop is required for of nuclear remodeling in iPSCs. None of the chromatin loop was detected in non-iPSCs. The pluripotency-related loop juxtaposes the enhancer and promoter regions to reactivate target genes. We also identified chromatin factor SMC1 as the key molecule for organizing the enhancer/promoter loop. This study thus identifies chromatin looping as a key epigenetic barrier that affects iPSC induction. Thus, further studies should be focused on the identification of other factors that can organize chromatin loops in order to promote iPSC induction.

Scientific Abstract:
Generation of induced pluripotent stem cells (iPSCs) by defined factors is an extremely inefficient process, because there is a strong epigenetic block preventing cells from achieving pluripotency. Here we report that virally expressed factors bound to the promoters of their target genes to the same extent in both iPSCs and unreprogrammed cells (URCs). However, expression of endogenous pluripotentcy genes was observed only in iPSCs. Comparison of local chromatin structure of the OCT4 locus revealed that there was a cohesin-complex-mediated intrachromosomal loop that juxtaposes a downstream enhancer to the gene's promoter, enabling activation of endogenous stemness genes. None of these long-range interactions were observed in URCs. Knockdown of the cohesin-complex gene SMC1 by RNAi abolished the intrachromosomal interaction and affected pluripotency. These findings highlight the importance of the SMC1-orchestrated intrachromosomal loop as a critical epigenetic barrier to the induction of pluripotency.